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ORIGINAL ARTICLE

Nine weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: final results of the phase III randomized Short-HER study‡

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Background: Chemotherapy plus 1-year trastuzumab is the standard adjuvant treatment of HER2-positive breast cancer. The efficacy of less extended trastuzumab exposure is under investigation. The short-HER study was aimed to assess the non-inferiority of 9 weeks versus 1 year of adjuvant trastuzumab combined with chemotherapy.

Patients and methods: HER2-positive breast cancer patients with node-positive or, if node negative, with at least one risk factor (pT>2 cm, G3, lympho-vascular invasion, Ki-67 > 20%, age ≤35 years, or hormone receptor negativity) were randomly assigned to receive sequential anthracycline–taxane combinations plus 1-year trastuzumab (arm A, long) or plus 9 weeks trastuzumab (arm B, short). This study was designed as a non-inferiority trial with disease-free survival (DFS) as primary end point. A DFS hazard ratio (HR) <1.29 was chosen as the non-inferiority margin. Analyses according to the frequentist and Bayesian approach were planned. Secondary end points included 2-year failure rate and cardiac safety.

Results: A total of 1254 patients from 82 centers were randomized (arm A, long: $n = 627$; arm B, short: $n = 626$). Five-year DFS is 88% in the long and 85% in the short arm. The HR is 1.13 (90% CI 0.89–1.42), with the upper limit of the CI crossing the non-inferiority margin. According to the Bayesian analysis, the probability that the short arm is non-inferior to the long one is 80%. The 5-year overall survival (OS) is 95.2% in the long and 95.0% in the short arm (HR 1.07, 90% CI 0.74–1.56). Cardiac events are significantly lower in the short arm (risk-ratio 0.33, 95% CI 0.22–0.50, $P < 0.0001$).

Conclusions: This study failed to show the non-inferiority of a shorter trastuzumab administration. One-year trastuzumab remains the standard. However, a 9-week administration decreases the risk of severe cardiac toxicity and can be an option for patients with cardiac events during treatment and for those with a low risk of relapse.

Trial Registration: EUDRACT number: 2007-004326-25; NCI ClinicalTrials.gov number: NCT00629278.

Key words: trastuzumab, adjuvant, breast cancer, cardiac safety, de-escalated treatment

Introduction

Adjuvant pivotal trials with 1 year trastuzumab have significantly improved the prognosis of HER2-positive early breast cancer, leading to the approval of 12 month administration as standard adjuvant treatment [1–4]. However, the selection of 1-year administration in these trials was largely empirical. Moreover, the patients entered into these pivotal trials had a higher risk of relapse, including mainly patients with node positive disease. In addition, a small Finnish study, where trastuzumab was administered for 9 weeks, produced a meaningful disease-free survival (DFS) benefit, with a favourable cardiac safety profile [5]. On these premises, the Short-HER study was designed to evaluate the non-inferiority of 9 weeks versus 1 year trastuzumab administered in combination with a standard anthracycline–taxane chemotherapy.

Methods

Study design

The Short-HER is a randomized, multicentric, investigator-driven study, supported by the Italian National Drug Agency (AIFA). The trial was approved by local ethical Committees, and conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. An independent data monitoring committee monitored the trial.

Participants

Women aged 18–75 with surgically resected, HER2-positive breast cancer, suitable for adjuvant chemotherapy were eligible. Women had to have node positivity, or in case of node negativity, at least one of the following features: pathological tumour size >2 cm, histological grade 3, presence of lympho-vascular invasion, Ki-67 > 20%, age ≤35 years, or hormone receptor negativity (ER and PgR < 10%). Normal liver, renal and marrow function was requested, as well as left ventricular ejection fraction (LVEF) within the institutional normal range. Patients with stage IIIB/IV disease were not eligible.

Procedures

Patients screening information, confirmation of eligibility and randomization was carried out through a Web-based system. A permuted-blocks randomization procedure was used, with patients stratified according to nodal status (0, 1–3, 4+), hormone-receptor status and regional coordinating centres.

Chemotherapy in arm A (long) consisted of AC (adriamycin 60 mg/sqm plus cyclophosphamide 600 mg/sqm) or EC (epidoxorubicin 90 mg/sqm plus cyclophosphamide 600 mg/sqm) administered every 3 weeks for four courses followed by paclitaxel 175 mg/sqm or docetaxel 100 mg/sqm every 3 weeks for four courses. Trastuzumab was administered every 3 weeks for 18 doses, starting with the first taxane dose (8 mg/kg loading dose at first cycle, and 6 mg/kg thereafter).

Chemotherapy in arm B (short) consisted of docetaxel 100 mg/sqm every 3 weeks for three courses followed by FEC (5-fluorouracil 600 mg/smq, epidoxorubicin 60 mg/sqm, cyclophosphamide 600 mg/sqm) administered every 3 weeks for three courses. Trastuzumab was administered weekly for 9 weeks, starting concomitantly with docetaxel (4 mg/kg loading dose at first week, and 2 mg/kg thereafter) (supplemental Figure S1, available at *Annals of Oncology* online). After protocol amendment, patients aged ≥65 years received docetaxel 80 mg/sqm in both arms.

LVEF measurements were repeated in arm A at the end of AC or EC chemotherapy, and in Arm B at the end of docetaxel-trastuzumab. In both arms, LVEF evaluations were repeated at 6, 9, 12, 18 months from randomization, and yearly thereafter.

When indicated, radiation therapy and hormonal therapy according to local standard were carried out at the end of chemotherapy. Follow-up including clinical examination, complete blood chemistry, chest radiogram and liver ultrasound were carried out every 6 months during the first 5 years and yearly thereafter. Mammography was repeated every 12 months.

The primary end point was DFS, calculated as the time between randomization and any of the following events, whichever first: local, regional and distant recurrence; contralateral breast cancer, excluding *in situ* carcinoma; other second invasive primary cancer; death before recurrence or second primary cancer. Overall survival (OS), calculated as the interval between randomization and patient death or last follow-up, was evaluated as second primary analysis outcome. The hazard ratio (HR) was used as measure of association for both the end points. It was estimated as the ratio between the hazard rate of events following short treatment and the hazard rate of events following long treatment.

Secondary end points included failure rate at 2 years (cumulative incidence of relapse, contralateral breast cancer, death for all causes, treatment withdrawal due to toxicity) and cardiac safety. Cardiac events were defined as decrease of LVEF >15 percentage points from basal values, or LVEF decrease >10 percentage points with absolute value below 50%, or symptomatic congestive heart failure, or other cardiac side-effects grade 2 or more according to NCI CTCAE version 3.

Statistical analyses

This study is designed to assess whether a shorter trastuzumab administration is non-inferior to the long one in respect with DFS. An HR <1.29 was set as a non-inferiority margin. The sample size was estimated by setting $\alpha = 0.05$ (one tail) and the power to 0.80, which resulted in 372 events and 2332 patients. However, a slower than expected rate of enrolment was observed, and, in order to comply to AIFA timelines, the sample size had to be reduced to 1252 patients. The data analysis was planned at the occurrence of the 198th event with a power of 0.56. HRs and its 90% confidence intervals for DFS and OS were estimated according to the Cox model. The Bayesian analysis was planned at the beginning of the study [6]. However, no a priori cut-off was pre-determined to consider the Bayesian analysis positive. For this analysis, a non-informative prior distribution was used.

For the evaluation of the 2-year failure rate, the measure of association used was the relative risk, which was estimated as the ratio between the risk of developing one of the events, whichever first, in the short treatment and the risk of the events in the long one.

Results

A total of 1254 patients from 82 centers were randomized to arm A (Long =627) and to arm B (Short =627); one HER2 negative patient erroneously randomized was excluded from treatment and analysis (supplement Figure S2, available at *Annals of*

Oncology online). The baseline characteristics were balanced between the two arms with a median age of 55 years, 54% of patients with node negative disease, and 68% with hormone receptor positive tumours (Table 1).

At a median follow up of six years, 200 DFS events were reported: 95 (15%) in the long and 105 (17%) in the short arm, respectively. Five-year DFS was 88% in the long and 85% in the short arm (Figure 1A). The estimated HR was 1.13 (90% CI 0.89–1.42) in the univariate Cox model with the upper limit of the CI crossing the non-inferiority margin set at 1.29. Sub-group DFS analysis according to age, stage, nodal status and hormone receptor status is represented in Figure 1C, and suggests that the short treatment might be inferior in stage III disease or in patients with 4+ positive nodes, although these differences are not statistically significant. This group of patients represents ∼16% of the entire patient population. DFS events distribution per treatment arm is reported in supplemental Table S1, available at *Annals of Oncology* online.

According to the pre-planned Bayesian analysis, which is based on the observed data, assuming a non-informative prior distribution, the posterior probability that the short arm is not inferior to the long one is 80% (Figure 1D).

The 5-year OS is 95.2% in the long (38 deaths) and 95.0% (40 deaths) in the short arm, HR 1.07 (90% CI 0.74–1.56) (Figure 1B).

Twenty-seven patients (4.3%) in the short-arm, and 82 (13.1%) in the long-arm experienced grade ≥2 cardiac adverse events (risk-ratio 0.33, 95% CI 0.22–0.50, $P < 0.001$) (Table 2). Figure 2 describes the time to cardiac event according to treatment arm, showing consistent results (HR =0.32, 95% CI 0.21–0.50; $P < 0.0001$).

The distribution of non-cardiac events was similar in the two arms (supplemental Table S2, available at *Annals of Oncology* online). Trastuzumab permanent discontinuation was reported in 53 (8.5%) patients in long arm and 21 patients (3.4%) in the short arm. The 2-year failure rate was 8.6% in the short and 9.4% in the long arm (risk-ratio 0.92, 95% CI 0.64–1.30).

Discussion

Notwithstanding the impressive results presented at the ASCO 2005 Meeting, which set 1 year trastuzumab as adjuvant treatment of HER2+ early breast cancer [2, 3], the question on treatment duration was still open. The empirical 1 year duration was not based on sound biological and/or pharmacological data and, in fact, the HERA trial was also exploring 2-year duration, with final results showing no benefit over 1 year [7].

At the same time, the FinHer trial had shown that 9 weeks trastuzumab could produce a significant decrease in risk of relapse

Table 1. Baseline patients characteristics, overall and by arm

Characteristics	Randomized	Short No. (%) 626	Long No. (%) 627	Overall No. (%) 1253
Age (at randomization)				
	<60	408 (65)	394 (63)	802 (64)
	≥60	218 (35)	233 (37)	451 (36)
	Median age (range)	55 (25-78)	55 (28-78)	55 (25-78)
Menopausal status				
	Premenopausal	221 (35)	227 (36)	448 (36)
	Postmenopausal	403 (64)	399 (64)	802 (64)
Pathological stage				
	I	264 (42)	245 (39)	509 (41)
	II	268 (43)	281 (45)	549 (44)
	III	91 (15)	100 (16)	191 (15)
Positive Lymph node				
	0	332 (53)	340 (54)	672 (54)
	1-3	194 (31)	189 (30)	383 (30)
	4+	100 (16)	98 (16)	198 (16)
Hormone-receptor status				
	Negative	199 (32)	201 (32.)	400 (32)
	Positive	427 (68)	426 (68)	853 (68)
HER2+ status				
	FISH+	103 (16.5)	96 (15.3)	199 (15.9)
	IHC2+/FISH+	95 (15.2)	91 (14.5)	186 (14.8)
	IHC3+	427 (68.2)	440 (70.2)	867 (69.2)
	Negative	1 (0.1)	0	1 (0.1)

FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry.

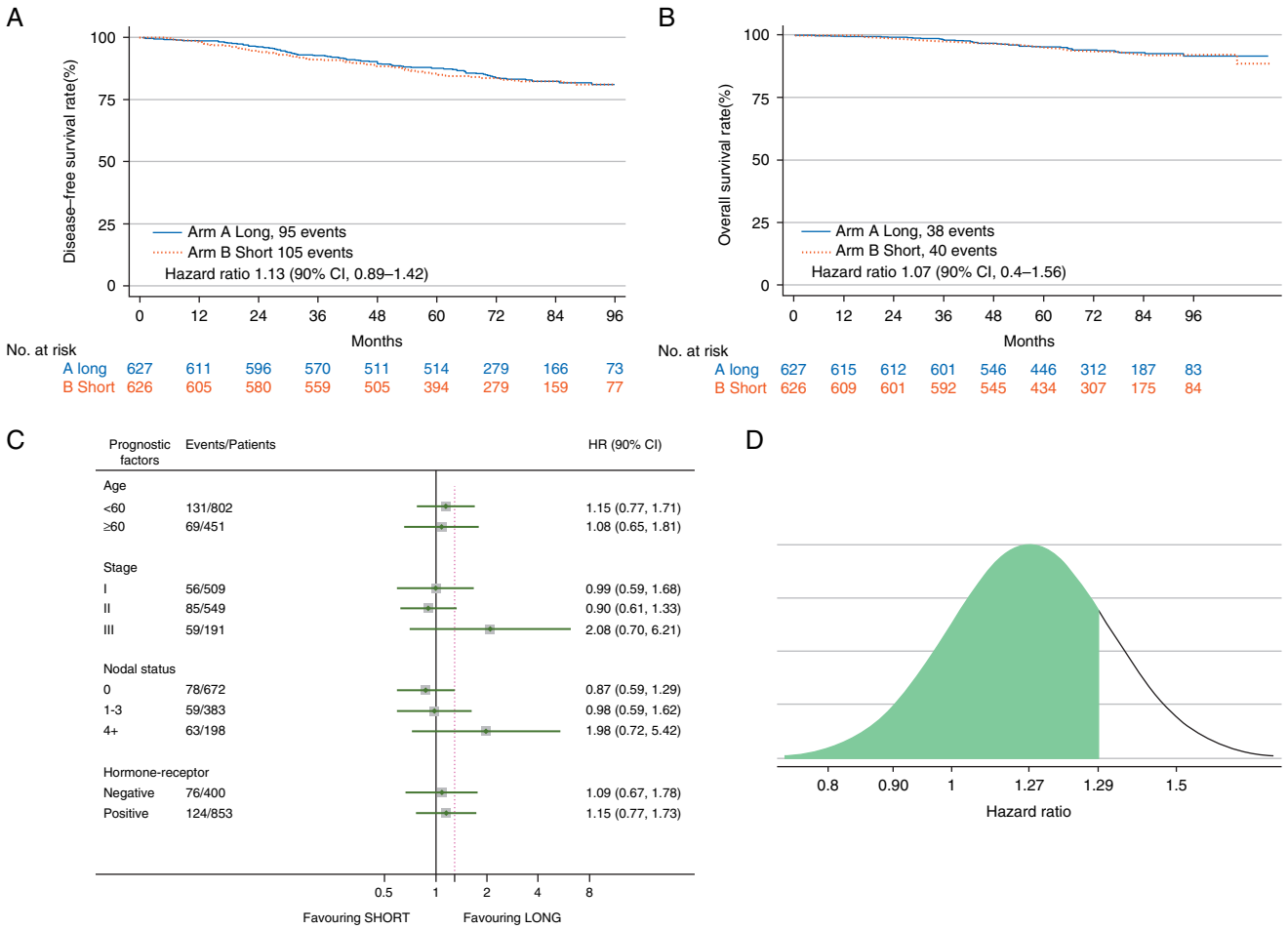

Figure 1. Study outcomes. (A) Kaplan–Meier plot of disease-free survival; (B) Kaplan–Meier plot of overall survival; (C) forest plot of disease-free survival; (D) posterior distribution of treatment effect on DFS, Bayesian analysis. Probability of short treatment to be non-inferior to long: 0.80. Prior distribution: not informative. The HRs were obtained by exponentiating the estimated logHRs. The *x*-axis uses the logarithmic scale.

[5]. Moreover, differently from real world population, these trials had recruited mostly patients with node positive disease and low risk of cardiac events. To address these issues, a network of academic and public hospitals in Italy designed the ShortHER trial funded by the Italian Drug Agency (AIFA). Based on the specific requirements of AIFA, ShortHER was designed as a non-inferiority trial comparing a long regimen versus a short one and both treatments had to be already available. The anthracycline–cyclophosphamide regimen followed by a taxane with concomitant 1 year trastuzumab based on B31 and N9831 data was chosen as the standard treatment while three courses of a taxane with 9 weeks of concomitant trastuzumab followed by three courses of FEC according to FinHER was the experimental arm. Therefore, the ShortHER trial compares not only different trastuzumab durations but also different chemotherapy regimens and the planned cumulative doses of epidoxorubicin were 180 and 360 mg/sqm in the short and long arm, respectively. The results of the ShortHER trial do not allow to claim non-inferiority being the HR 1.13 with the upper limit of CI crossing the pre-defined boundary set at 1.29. Although underpowered, this study can provide some important information. First of all, the characteristics of the patients in the ShortHER trial are different in comparison to those of the patients entered into the pivotal trials with median age 55 years versus <50 years, and 54% node negative disease versus 0%–32%, respectively. These characteristics are associated with a higher risk of cardiac events and lower risk of disease relapse. In fact, although the definition of cardiac

Table 2. Cardiac adverse events (AEs) of grade ≥2

Cardiac events	Short ($n = 626$)	Long ($n = 627$)
	No. of patients with cardiac events (%)	
Total	27 (4.3)	82 (13.1)
Grade max		
2	19 (3.0)	64 (10.2)
3	5 (0.8)	15 (2.4)
4	3 (0.5)	3 (0.5)
Age		
<60	17 (2.7)	52 (8.3)
≥60	10 (1.6)	30 (4.8)

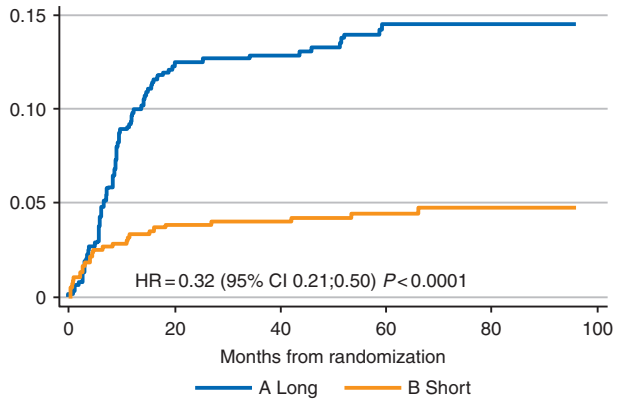

Figure 2. Cumulative hazard estimates for cardiac adverse events.

toxicity differs across trials, the incidence of cardiac events in the pivotal trials was lower (ranging from 1.6 to 4.4 in N9831, B31 and HERA trials) than that observed in ShortHER. Our data, however, are more in line with those reported from large population studies of patients treated with adjuvant trastuzumab [8–10] and show that a short treatment is associated with a significantly lower cardiac toxicity. As far as risk of relapse is concerned, no outcome difference in treatment arms has been observed in patients with 0–3 positive nodes (~85% of our patient population) while 1-year trastuzumab seems to be associated with a better outcome, although not significant, in stage III or 4+ positive nodes patients.

Finally, according to the pre-planned Bayesian analysis, the probability that a short treatment is not inferior to the long one is 80%, supporting that the hypothesis of non-inferiority cannot be ruled out.

The issue of treatment de-escalation is an increasingly relevant topic due to the availability of more effective treatments and more favourable patient outcomes.

Some trials have addressed the de-escalation of chemotherapy. BCIRG006 compared AC-docetaxel (AC-T) versus AC-docetaxel + trastuzumab (AC-TH) versus docetaxel–carboplatin + trastuzumab (TCbH) and, while confirming the superiority of trastuzumab, proved that the non-anthracycline TCbH regimen had a better cardiac tolerability (despite a 3% DFS difference favouring the AC-TH arm) [4].

Two single arm phase II trials evaluated 12 weeks of paclitaxel (APT trial) or four courses of docetaxel/cyclophosphamide (TCH trial) [11–13]. These trials mainly included patients at very low risk, showed an extremely low relapse rate and these regimens have been adopted and recommended in clinical practice for low-risk patients.

De-escalated trastuzumab duration was addressed by the Phare, SOLD and PERSEPHONE trials.

In the Phare trial, 3384 patients were randomised to receive trastuzumab for 1 year versus 6 months; trastuzumab was given either sequentially or concomitantly with chemotherapy. The trial could not demonstrate the non-inferiority of 6 months trastuzumab in the overall patient population [14]. However, a subgroup analysis showed that a prognostic score based on nodal status and T size, could identify a low-risk group of patients, representing about one-third of the study population, with such a good prognosis that the clinical value of 1 year trastuzumab could be questionable [15].

In the SOLD trial, 2100 patients were randomised to receive trastuzumab for 1 year or for 9 weeks [16]. Differently from our trial, the chemotherapy regimen was identical in the two treatment arms. Again, non-inferiority could not be claimed being the 5 year DFS estimates 90.5% in long versus 88.0% in short arm. Of interest, however, the 5 year distant DFS was very similar (94.2% in long and 93.2% in short) while the cardiac toxicity was significantly higher in case of 1 year trastuzumab (36 versus 21 cases of congestive heart failure).

The PERSEPHONE trial randomised 4089 HER2+ patients to receive trastuzumab for 6 months or 1 year. At a median follow-up of 4.9 years, the 4 years DFS was 89% in both arm with an HR of 1.05 (confidence intervals included in the definition of non-inferiority). Treatment interruptions due to cardiac events were 4% in the 6 months arm and 8% in the 1 year arm ($P < 0.0001$) [17].

Phare, SOLD and ShortHER, can be considered non-conclusive, not having proved non-inferiority, while the larger PERSEPHONE study has proved the non-inferiority of 6 months trastuzumab. Noteworthy, all the four trials have consistently shown that a significant proportion of patients is at low risk of relapse and a shorter trastuzumab treatment administration would not compromise the outcome, while reducing the risk of cardiac events. This information is clinically relevant as up to 8% of patients in pivotal trials could not start trastuzumab and up to 15% had to discontinue trastuzumab because of cardiac events [18–20].

In conclusion, the non-inferiority of 9 weeks trastuzumab cannot be claimed on the basis of the frequentist approach. However, a shorter trastuzumab administration could be an option for those patients who experience cardiac events and for those with a low risk of relapse. Moreover, this regimen might facilitate the access to trastuzumab to patients living in countries with limited resources. Finally, a planned meta-analysis of individual patient data from randomised trials, will allow to identify subgroups of patients in which a shorter treatment can provide equivalent outcomes with lower toxicity.

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References

1. Moja L, Tagliabue L, Balduzzi S et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev 2012; 18: CD006243.
2. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER-2 positive breast cancer. N Engl J Med 2005; 353(16): 1659–1672.
3. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER-2 positive breast cancer. N Engl J Med 2005; 353(16): 1673–1684.
4. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011; 365(14): 1273–1283.
5. Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006; 354(8): 809–820.
6. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. The Atrium, Southern Gate, Chichester, England: John Wiley & Sons, Ltd; 2004.
7. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet 2013; 382: 1021–1028.
8. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Heart Assoc 2014; 3(1): e000472.
9. Thavendiranathan P, Abdel-Qadir H, Fischer HD et al. Breast cancer therapy-related cardiac dysfunction in adult women treated in routine clinical practice: a population-based cohort study. J Clin Oncol 2016; 34(19): 2239–2246.
10. Vaz-Luis I, Keating NL, Lin NU et al. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol 2014; 32: 927–934.
11. Tolaney SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015; 372(2): 134–141.
12. Jones SE, Collea R, Paul D et al. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. Lancet Oncol 2013; 14: 1121–1128.
13. Tolaney SM, Barry WT, Guo H et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). J Clin Oncol 2017; 35(Suppl 15): 511.
14. Pivot X, Romieu G, Debled M et al. PHARE trial investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol 2013; 14(8): 741–748.
15. Kramar A, Bachelot T, Madrange N et al. Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial. Ann Oncol 2014; 5: 1563–1570.
16. Joensuu H, Fraser J, Wildiers H et al. Effect of adjuvant trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2-positive breast cancer: the SOLD randomized clinical trial. JAMA Oncol 2018; 4: 1199–1206.
17. Earl HM, Hiller L, Vallier AL et al. PERSEPHONE: 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: randomized phase 3 non-inferiority trial with definitive 4-yr disease-free survival results J Clin Oncol. 2018; 36(Suppl); abst 506.
18. Perez EA, Suman VJ, Davidson NE et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008; 26(8): 1231–1238.
19. Suter TM, Procter M, van Veldhuisen DJ et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 2007; 25: 3859–3865.
20. Tan-Chiu E, Yothers G, Romond E et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human Epidermal Growth Factor Receptor 2–overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005; 23: 7811–7819.

Appendix

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